A Triply Convergent Total Synthesis of a Symchiral† Pyrrolidine-Fused Prostacyclin Analog‡

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The synthesis of symchiral 1-azatricyclo[6.3.0.0^{2,6}]undeca-5-enyl prostaglandin I_2 analog **34** is reported. Construction of the tricyclic skeleton of **34** was accomplished in two steps by employing a triply convergent approach which utilized vinyl sulfone technology. Introduction of the heterocyclic subunit of **34** was achieved by an S_N2'–thio-Claisen rearrangement which efficiently coupled a thiolactam moiety to a suitable allylic vinyl sulfone. Annulation of bicyclic vinyl sulfones **20**, **23**, and **29** was accomplished *via* a conjugate addition of lithium acetylide **11** to the vinyl sulfone moieties, followed by an intramolecular S_N2 displacement of a suitable nucleofuge. Competition between intramolecular carbon alkylation and β-elimination of stabilized nitrogen anions from intermediate α-sulfonyl anions **20-i**, **23-i**, **29-i** was discussed. Refunctionalization of the resulting tricyclic skeleton was accomplished by employing standard literature protocols. Compound **34** was found to be essentially inactive as an inhibitor of collagen-induced platelet aggregation, having an IC_{50} of >10 μM.

Introduction

Since its isolation by Vane in 1976,[1] prostacyclin (PGI_2, **1**) has served as a focal point for investigation, from both synthetic and clinical standpoints.[2] In the initial report of this prostanoid, Vane disclosed that PGI_2 is the most potent endogenous inhibitor of blood platelet aggregation known, being approximately 30 times more active than another potent inhibitor, prostaglandin E_2. Unfortunately, its short *in vivo* half-life (*ca.* 3.0 min) precludes its practical application as a clinical agent.

In an initial effort at addressing prostacyclin's metabolic instability, the C-9 oxygen atom of **1** was replaced with a methylene unit, due to the known hydrolytic sensitivity of the enol ether moiety. In spite of this slight structural modification, carbacyclin **2** possesses only 10% of the activity of prostacyclin,[2] and yet it has approximately the same *in vivo* half-life as **1** due to the enzymatic oxidation of the allylic alcohol by C-15 dehydrogenase.[3] Second-generation analogs of **1** have circumvented this problem by introducing sterically demanding groups near C-15. Recent studies have also revealed that further metabolic deactivation of **1** is accomplished by the enzymatic oxidation of C-3;[4,5] however, third generation derivatives of prostacyclin, such as cicaprost[4] and U68,215,[5] have featured replacement of the problematic methylene unit with an oxygen atom to avoid this problem.

Recently, we have reported the preparation and testing of a series of arene-fused prostaglandin I_2 analogs **3**–**8**[6] which were designed to probe the volume of space accessible by the terminal carboxylic acid moiety (Scheme 1). These materials inhibited collagen-induced platelet aggregation (IC_{50}) over a range of 10^4, allowing us to formulate additional targets based upon computer modeling. Of considerable interest was the finding that compound **3** was also an extremely potent inhibitor of neutrophil activation[7] which suggested a possible role as an adujvant in the treatment of reperfusion injury in post-CPR patients by virtue of inhibition of neutrophil activation within the ischemic myocardium.[8]

While previous studies within these laboratories have focused upon the synthesis and testing of carbocyclic derivatives of **1**,[6] it was felt that the 10-fold activity difference between PGI_2 and carbacyclin merited giving consideration to the reintroduction of a heteroatom substituent at the C-9 position. It was hypothesized that the oxygen atom of **1** may be serving as an additional hydrogen bonding site at the PGI_2 receptor; thus, by reintroducing a heteroatom at C-9, it may be possible to enhance the binding of our model. Accordingly, azatricyclic derivative **9** was proposed as a synthetic target. Molecular modeling studies of **9** using Tektronik's CAChe software and employing MM2 parameters revealed that the pyrrolidine derivative provided good structural over-

† For a definition of symchiral as an alternative to "homochiral" meaning chiral nonracemic see: Taber, D. F. *Chem. Eng. News* **1991**, 5.

‡ Syntheses Via Vinyl Sulfones. 58.

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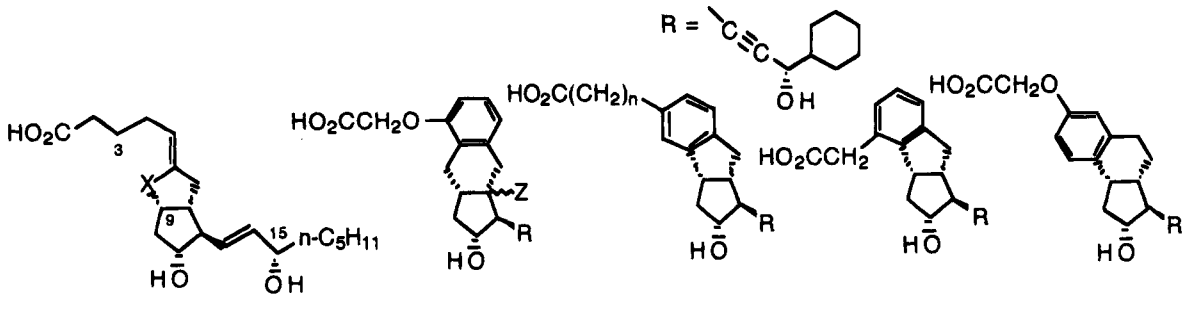
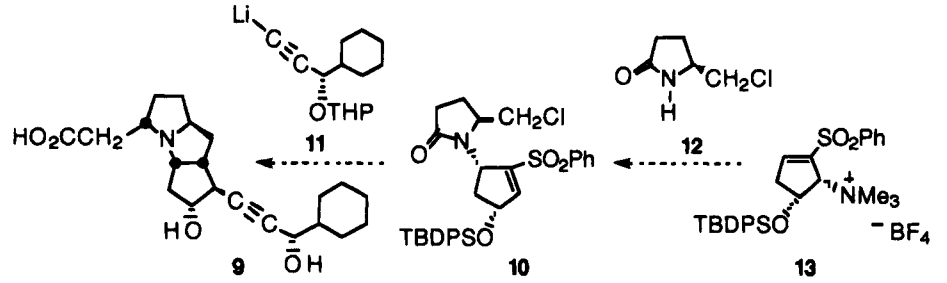
Scheme 1



1 X=O Prostacyclin (PGI_2) 2 nM
2 X=CH_2 Carbacyclin 20 nM
3 Z = H_β (cis) 3 nM
4 Z = H_α (trans) 52 nM
5 n=1 180 nM
6 n=2 330 nM
7 2,500 nM
8 > 10,000 nM

Scheme 2



lap with our model, and accordingly synthesis and testing of **9** was pursued.

Results and Discussion

The original strategy chosen for the synthesis of pyrrolidine **9** is shown in Scheme 2. In keeping with existing methodology, a triply convergent synthesis of **9** was envisioned employing vinyl sulfones in key bond-forming reactions. Precedence for such an approach was established by our previously reported synthesis of *d*-carbacyclin.[9] Thus, following functional group interconversions, tricyclic amino acid **9** was thought to derive from the conjugate addition of symchiral lithium acetylide **11**[10] to bicyclic vinyl sulfone **10** in a protocol similar to those previously reported from our laboratories.[11] Ultimately, introduction of the heterocyclic subunit of **10** was to be achieved by the S_N2' reaction of symchiral pyrrolidinone **12**[12] with symchiral ammonium salt **13**.[13]

Thus, (*S*)-5-(hydroxymethyl)-2-pyrrolidinone (**14**) was prepared from (*S*)-glutamic acid in two steps and in 60% yield according to the procedure of Silverman and Levy.[14] Next, treating alcohol **14** with NCS and Ph_3P[15] for 12 h led to the isolation of symchiral chloride **12** in 84% yield. Reacting **12** with 1 equiv of NaHMDS at 0 °C resulted in the formation of its sodium salt which was then further cooled to −78 °C and subsequently treated with ammonium salt **13** to afford bicyclic lactam **10** in 95% yield and with a regio- and stereoselectivity of ≫95:5.

With the requisite annulation precursor in hand, it was next left to determine the feasibility of performing the tandem addition−cyclization reaction on this substrate. While there was ample precedence for the success of this transformation when carbocyclic systems were examined,[6,9] there was considerable concern as to whether the annulation event would be sufficiently fast to compete with a potential β-elimination of the lactam anion. Thus, treating **10** with an ether/HMPA solution of lithium acetylide **11** at −78 °C failed to provide the desired tricyclic lactam and permitted only poor recovery of the starting material (*ca.* 30%). However, despite the poor mass balance of this reaction, there was no evidence to suggest that the S_N2' reaction was in competition with the required annulation event. Neither raising the temperature of the reaction nor increasing the number of equivalents of lithium acetylide **11** significantly altered the outcome of this reaction. More reactive organometallics, such as MeLi or the corresponding potassium acetylide of **11**,[16] were also employed in this reaction; however, these nucleophiles also failed to undergo fruitful addition to **10**.

It was unclear at this stage of the investigation as to the exact reason why **11** failed to undergo addition to vinyl sulfone **10**. One potential complication may have been the abstraction of a proton adjacent to the carbonyl to generate the lactam enolate; however, this did not appear to be a competitive pathway, as quench of these reactions with D_2O failed to demonstrate significant deuterium incorporation in recovered **10**. In addition, employing a large excess of **11** (3−4 equiv) should have compensated for any anion quench due to proton abstraction; however, these experiments also failed to provide the requisite tricyclic lactam. These results seem to suggest that the initial addition of **11** to the vinyl sulfone moiety is the problematic step. In an effort to ascertain the difficulties associated with this reaction, molecular modeling studies were performed on **10**; however, these studies failed to suggest a viable explanation for the

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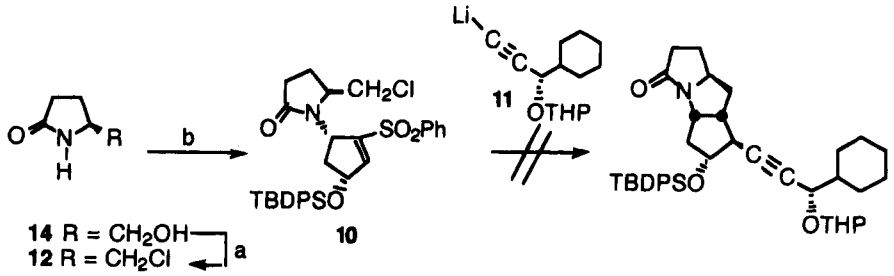
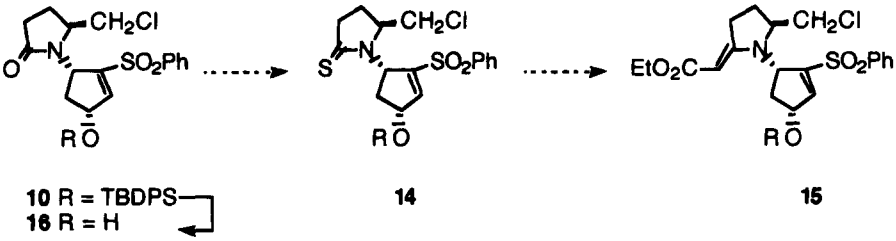
Scheme 3[a]



[a] Reagents and conditions: (a) NCS, Ph_3P, CH_2Cl_2, rt, 12 h, 84%; (b) NaHMDS, THF, 0 °C, 1 h, then cooled to −78 °C and added **13**, 1 h, 95%; (c) **11**, Et_2O/HMPA, −78 °C, 1 h.

Scheme 4



intractable nature of this substrate. With the lack of supporting evidence, it was hypothesized that stereoelectronic effects present in **10** were somehow lowering the reactivity of the vinyl sulfone moiety and thus preventing organometallic reagents from performing their initial attack (Scheme 3).

Given the necessity of eventual transformation of the amide carbonyl to install the carboxylic acid upper side chain of **9**, our attention next turned to the possibility of employing either the corresponding thiolactam **14** or the vinylogous urethane **15** as substrates in the tandem addition−cyclization reaction. Accordingly, treatment of **10** with Lawesson's reagent[17] in benzene or xylene at reflux failed to provide the requisite thiolactam, lactam alcohol **16** being recovered in low yield (*ca.* 20%). Moreover, it was found that prolonged heating of **10** led to its eventual decomposition under these reaction conditions. Alternative reagents for the conversion of lactams to their corresponding thio derivatives were also investigated, including P_4S_{10}[18] and various Lawesson's reagent analogs;[19] however, these protocols failed to provide the requisite thiolactam. Even attempts at activating the carbonyl with $POCl_3$, triphosgene, or oxalyl chloride, followed by subsequent trap of the intermediate chloroiminium ion with TMS_2S,[20] failed to afford **14**. It can only be assumed that steric hindrance at the lactam carbonyl prevented this substitution reaction. These results are summarized in Scheme 4.

Given our inability to refunctionalize the skeleton of **10**, it became necessary to reevaluate the synthetic route to **9**. We were confident that a bicyclic vinyl sulfone similar in structure to either **10**, **14**, or **15** was required, but obtaining these systems directly from **10** was problematic. The necessity of thiolactam **14** as a synthetic precursor to vinylogous urethane **15** impelled exploration of alternative routes to the requisite thiolactam. One particularly interesting prospect suggested itself upon the examination of the works of Gommper,[21] Yoshida,[22] and Yamazaki.[23] These authors reported that thioamides and thiolactams, upon treatment with allylic halides, undergo sulfur alkylation to provide *S*-allyl thioimidates which subsequently undergo a S → N thio-Claisen rearrangement resulting in the formation of the corresponding *N*-allyl derivatives.

This precedent suggested that reacting thiolactam **18** with sulfone-bearing allylammonium salt **19** would allow construction of bicyclic vinyl sulfone **20**. Symchiral vinyl sulfone **19** was readily available from our previous studies on the total synthesis of PGE_2.[24] Therefore, lactam **12** was converted to thiolactam **18** in 80% yield employing Lawesson's reagent. Treating **18** with 1 equiv of NaHMDS at 0 °C for 1 h generated its sodium salt which, upon cooling to −78 °C, was reacted with ammonium salt **19** to afford a 1:1 mixture of regioisomeric bicyclic thiolactams **20** and **21** in 86% yield.

Although the percent conversion of this reaction was quite satisfactory, the low level of regioselectivity was disconcerting. It was postulated that thiolactam **21** arose from a second S_N2' attack of a molecule of **18** on thioimidate intermediate **i**, followed by thio-Claisen rearrangement of intermediate **ii** (Scheme 5). In an effort to improve the regioselectivity of this reaction, it was elected to lower the reactivity of the thiolactam

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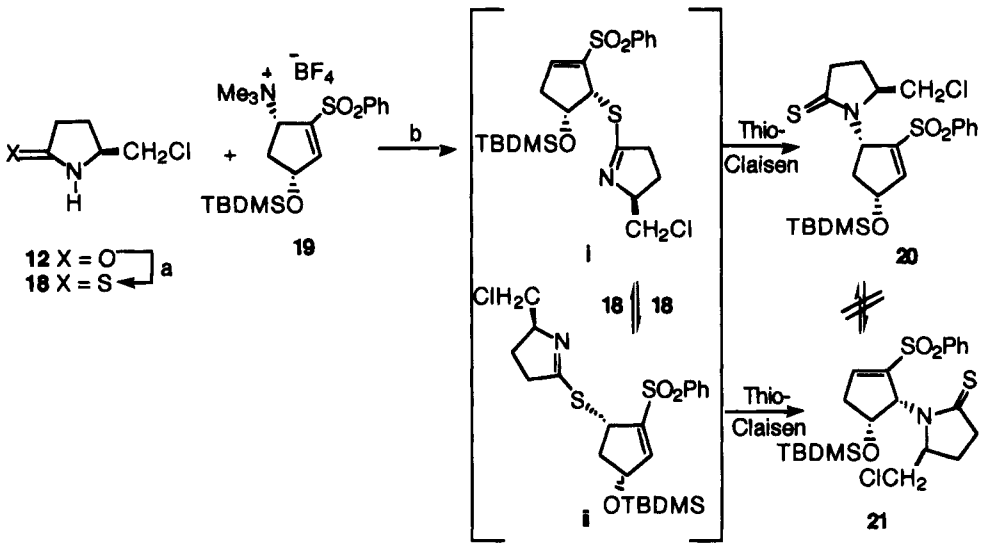
Scheme 5[a]



[a] Reagents and conditions: (a) Lawesson's reagent, C_6H_6, rt, 12 h, 80%; (b) NaHMDS, THF, 0 °C, 1 h, then cooled to −78 °C and added **19**, 5 min, 86%.

nucleophile by employing the neutral species, rather than its sodium salt. Accordingly, treating ammonium salt **19** with neutral thiolactam **18** in CH_2Cl_2 for 12 h exclusively afforded bicyclic thiolactam **20** in 92% yield.

While this result was quite satisfying, it was felt that employing ammonium salt **19** in this transformation was needlessly wasteful since mesylate **22** is an intermediate in the synthesis of **19**, and it was expected that it would react identically to the ammonium salt.[23] As a testimony to the extravagance of employing ammonium salt **19**, it should be noted that the conversion of mesylate **22** to **19** requires four steps with an 80% overall yield. Another serious concern was that the coupling of neutral **18** with these vinyl sulfone derivatives requires significantly longer reaction times. This consideration could prove to be problematic upon scale-up, as it was known from previous studies in these laboratories that ammonium salts **13** and **19** undergo isomerization to afford complex mixtures of regio- and stereoisomeric ammonium salts which could conceivably lower the selectivity of this reaction.[23] Mesylate **22** is known to be a stable isolable intermediate and, thus, should not be prone to isomerization.

Accordingly, mesylate **22** was treated with neutral thiolactam **18** in CH_2Cl_2 at −78 °C, and the reaction mixture was gradually warmed to room temperature over 12 h to afford a gelatinous mass which, upon basic workup, provided a 4:1 mixture of bicyclic thiolactams **20** and **21** in 58% yield. Addition of a small quantity of poly(vinylpyridine) (PVP) to the reaction mixture circumvented formation of the gelatinous reaction mixture and improved the overall conversion of the reaction to 82%; regrettably, no change was observed in the relative ratio of **20** to **21**. Maintaining the reaction temperature at −78 °C for longer time intervals prior to warming only served to slightly alter the relative ratio of these products (~5:1 in favor of **20**), and this change in the temperature profile incurred significantly longer reaction times (>24 h).

Changing the reaction medium to less polar solvent systems appeared to favorably influence the ratio of the reaction products. Substituting benzene for methylene chloride, albeit at a much higher initial reaction temperature (~6 °C), resulted in the formation of a mixture of bicyclic thiolactams in yields comparable to those obtained in CH_2Cl_2 but with only a slightly improved regioselectivity: 5.5:1 (**20**:**21**). Employing toluene as a solvent permitted much lower initial reaction temperatures (−78 °C) and, upon gradual warming to room temperature, provided a mixture of the bicyclic thiolactams in 84−88% yield and with relative ratios typically ranging between 9 and 11:1 (**20**:**21**). In all instances where neutral thiolactam **18** was used, it was necessary to employ PVP as an acid scavenger to ensure high levels of conversion, and typical reaction times ranged between 14 and 24 h for completion. Overall, application of mesylate **22** in this transformation proved to be more efficient than employing ammonium salt **19** in spite of the slightly lower yields and levels of regioselectivity obtained. This protocol also proved amenable to scale-up with little to no loss of either yield or regioselectivity (Scheme 6).

With the required thiolactam in hand, it was time to convert **20** to its corresponding vinylogous urethane **23**. Accordingly, treating thiolactam **20** with either ethyl bromo- or ethyl iodoacetate in acetonitrile failed to provide the requisite iminium ion intermediate necessary for the Eschenmoser episulfide contraction.[25] Alternatively, employing the corresponding triflate[26] in acetonitrile led to smooth alkylation of **20**, and subsequent treatment of this iminium ion with Ph_3P and Et_3N under conditions reported by Rapoport[27] led to the formation of vinylogous urethane **23** in 87% yield, as a single olefin isomer. The geometry of this vinylogous urethane was tentatively assigned as the *E*-isomer; however, no attempt was made to rigorously assign its stereochemistry due to the anticipated loss of this stereocenter in later steps of this synthesis (Scheme 6).

With sufficient quantities of the requisite cyclization precursors available, it was appropriate to construct the tricyclic skeleton of **9**. Treating bicyclic vinylogous

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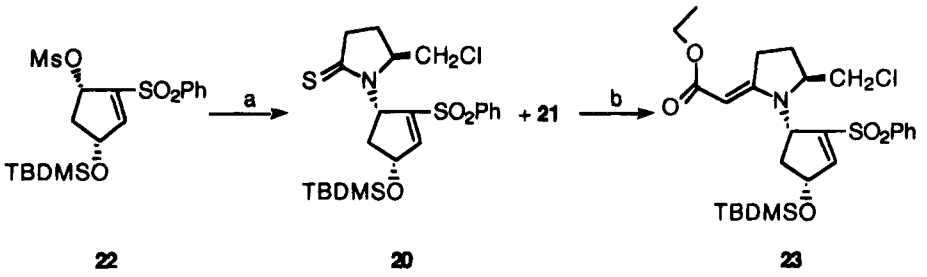
Scheme 6[a]



22 20 23

[a] Reagents and conditions: (a) **18**, PVP, toluene, −78 °C to rt, 14 h, 84% of **20**; (b) (i) $TfOCH_2CO_2Et$, CH_3CN, 0 °C, 2 h; (ii) Ph_3P, CH_2Cl_2, 10 min; (iii) Et_3N, 12 h, rt, 87%.

urethane **23** with 1 equiv of lithium acetylide **11** in ether/HMPA at 0 °C for 1.5 h led to the isolation of enyne **25**, along with an inseparable mixture of starting material and desired tricyclic sulfone **24** in 18%, 30%, and 17% yields, respectively. While this reaction had failed to reach completion, no products corresponding to the anticipated S_N2' displacement of the vinylogous urethane ring system were observed; thus, we were hopeful that conditions might be found which would eliminate the formation of **25**, and yet allow for the complete consumption of **23**.

Initially, it was hoped that formation of enyne **25** might be circumvented by changing the reaction temperature. Repeating this reaction at lower temperatures appeared to slow the rate of the competitive sulfinic acid elimination pathway; however, the rate of formation of **24** was also slowed, therefore providing only a moderate increase in the conversion of **23** to **24** (35% yield). As expected, higher reaction temperatures favored formation of enyne **25**. Employing 2 equiv of lithium acetylide **11** while rigorously maintaining the reaction temperature at −30 °C significantly improved the conversion of **23** to **24** (*ca.* 70%), while the formation of **25** was reduced to ≤10%, *provided* short reaction times were employed (<20 min). Optimum conditions were achieved by quickly transferring an ethereal solution containing 3.0 equiv of both lithium acetylide **11** and HMPA at −30 °C *via* cannula to vinyl sulfone **23** and allowing the resulting reaction mixture to stir for 15 min. By utilizing this strategy, it was ensured that tricyclic sulfone **24** could be routinely obtained in yields ranging between 82 and 90%, while enyne **25** was typically produced in <7% yield. While employing a large excess of **11** seems wasteful, the unreacted acetylene was readily and reproducibly recovered and recycled in approximately 90% yield.

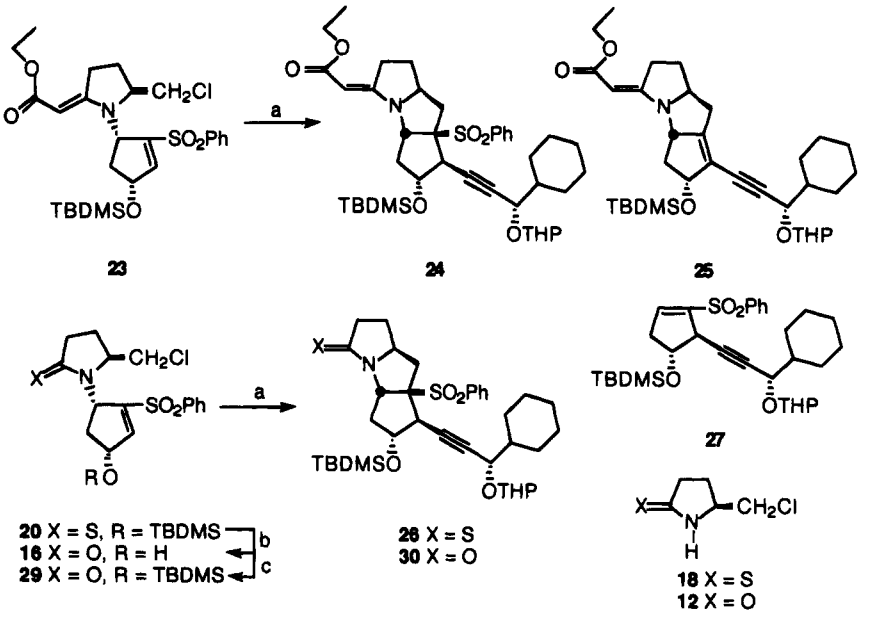
While it was gratifying that **23** underwent the desired tandem addition−annulation reaction to good advantage with no evidence of the anticipated S_N2' displacement of the vinylogous urethane ring system, it was still puzzling that this system successfully underwent this transformation while bicyclic lactam **10** had failed to undergo any appreciable reaction except for slow degradation. Save for the obvious difference associated with the heterocyclic rings, the only other distinction between these molecules was the specific silyl ether protecting group attached to the C-11 oxygen. In order to better understand this apparent dichotomy, it was elected to subject both bicyclic thiolactam **20** and the corresponding lactam **29** to conditions which favored the tandem addition−annulation reaction of **23** and determine whether this difference in protecting groups accounted for the differential reactivity.

Treating thiolactam **20** with 1.2 equiv of benzene seleninic anhydride[28] for 4 h at room temperature resulted in the formation of lactam alcohol **16** in 76% yield. Unwanted deprotection of the silyl ether moiety appeared to be unavoidable. Employing alternative protocols, such as *m*-CPBA,[29] *m*-CPBA buffered with Na_2HPO_4, or simply with $Hg(OAc)_2$[30] under hydrolytic conditions, also resulted in the formation of lactam alcohol **16**, albeit in much lower yields, while treatment with activated MnO_2[31] failed to provide any appreciable reaction. Conversion of alcohol **16** to TBDMS ether **29** was smoothly effected via treatment with excess TBDMS-triflate and Et_3N. Silyl ether **29** did not prove to be amenable to storage as it was noted that this substrate had a short shelf life (~10 days) during which time it gradually reverted back to alcohol **16**. Therefore, freshly prepared silyl ether **29** was routinely employed in the annulation studies.

Accordingly, both thiolactam **20** and lactam **29** were individually subjected to the tandem addition−cyclization reaction conditions which were found to be successful for vinylogous urethane **23**. Thus, treating either **20** or **29** with 3.0 equiv of lithium acetylide **11** in ether/HMPA at −30 °C for 15 min led, in both cases, to the formation of three significant products. In the reaction of thiolactam **20**, the desired tricyclic thiolactam **26** was isolated in 63% yield along with acetylenic vinyl sulfone **27** and monocyclic thiolactam **18** in 9% and 10% yields, respectively. Vinyl sulfone **27** undoubtedly results from a stepwise process where the initial conjugate addition adduct undergoes β-elimination competitive with intramolecular alkylation. In addition to the aforementioned compounds, a myriad of less polar products were isolated and tentatively identified as compounds resulting from the addition of a second equivalent of lithium acetylide **11** to vinyl sulfone **27**. Assignment of these products was not undertaken due to the comparatively small amounts of this material obtained (≤5%) and the complexity of this mixture due to the presence of THP diastereomers (Scheme 7). Likewise, treatment of lactam **29** with lithium acetylide **11** resulted in the formation of three reaction products: tricyclic lactam **30**, monocyclic lactam **12**, and vinyl sulfone **27**, which were obtained in 51%, 22%, and 19% yields, respectively. Once again, a number of less polar reaction products resulting from the conjugate addition of **11** to **27** were observed (Scheme 7).

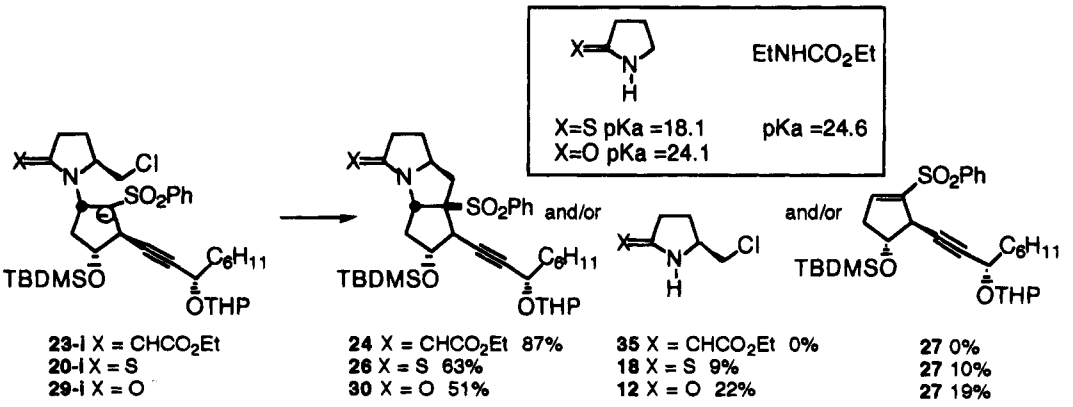
(28) Cussans, N. J.; Ley, S. V.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1651.
(29) Kochhar, K. S.; Cottrell, D. A.; Pinnick, H. W. *Tetrahedron Lett.* **1983**, *24*, 1323.
(30) Davies, S. G.; Mortlock, A. A. *Tetrahedron Lett.* **1991**, *32*, 4791.
(31) Rani Rani, B.; Rahman, M. F.; Bhslerao, U. T. *Tetrahedron* **1992**, *48*, 1953.

Scheme 7[a]



[a] Reagents and conditions: (a) **11**, Et_2O/HMPA, −30 °C, 15 min; for vinylogous urethane **23**, **24** in 87% yield; for thiolactam **20**, **26** in 63% yield; for lactam **29**, **30** in 51% yield; (b) benzene seleninic anhydride, THF, rt, 4 h, 76%; (c) TBDMS−OTf, Et_3N, CH_2Cl_2, 0 °C.

Scheme 8



These results are somewhat puzzling, particularly when compared to the failure of **11** to undergo conjugate addition to vinyl sulfone **10** (Scheme 3). While it might be argued that addition of acetylide anion **11** to the sterically more demanding TBDPS ether **10** is retarded by the bulky silyl ether protecting group at C-11, this explanation is not satisfying in light of successful addition of **11** to analogous vinyl sulfones bearing α-face alkyl and aryl groups at C-9 as well as the bulky C-11 *tert*-butyldiphenyl silyl ether.[6]

A significant aspect of this study concerns the tandem addition−annulation reactions of bicyclic compounds **20**, **23**, and **29** (Scheme 8). Intermediate α-sulfonyl anions (**20-i**, **23-i**, **29-i**) undergo competition between β-elimination of the stabilized nitrogen-centered anion and intramolecular alkylation at the chloromethyl moiety. The partitioning ratios observed do not appear to be a simple function of the heterocycle's ability to act as a nucleofuge. Bordwell has shown that thioamides, including five-membered ring analogs[32] (see box Scheme 8) are 6−7 pK_a units more acidic than the corresponding amides.[33]

While the pK_a for vinylogous urethane **35** is currently unknown, the value of 24.6 for the indicated ethylcarbamate[32] would arguably be an upper limit. Therefore, an argument based upon pK_a's might anticipate that either the vinylogous urethane moiety or the thiolactam unit would serve as a better leaving group than lactam **12**. Since these expectations are contrary to the experimental results, it would appear that conformational factors of the heterocyclic ring are of crucial importance in determining the alkylation/elimination ratio.

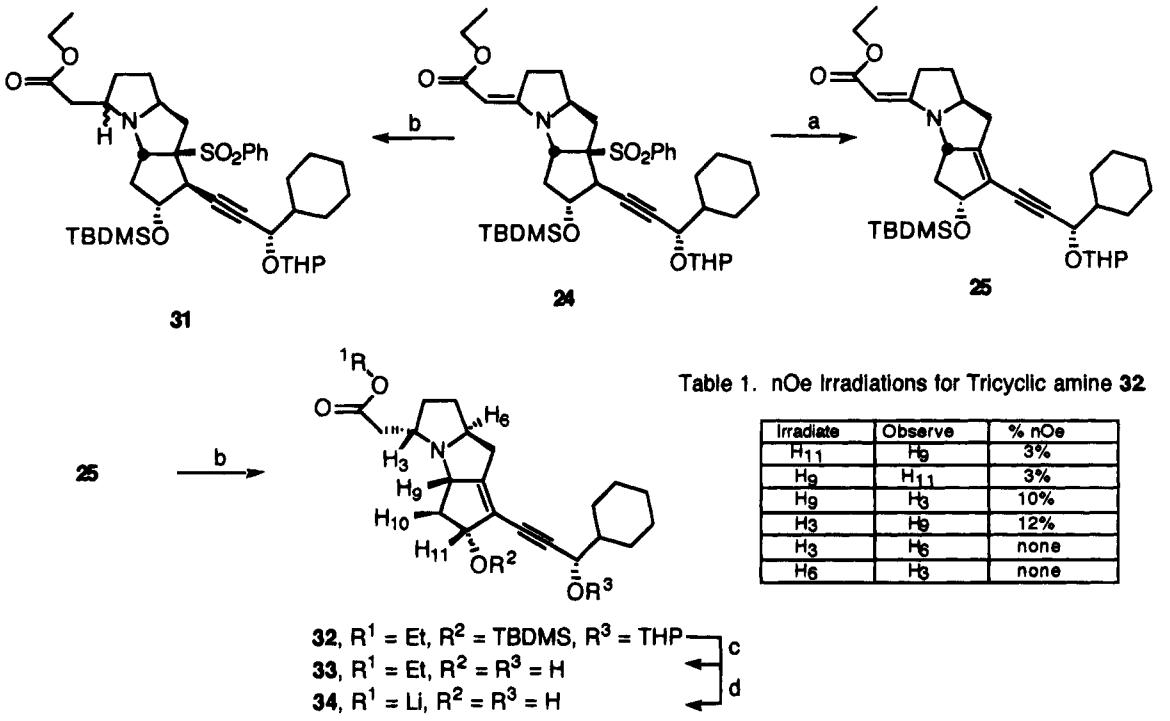
Hence, in an effort to develop a plausible rational of these observations, a series of MM2 calculations were performed on the ground state conformations of these systems.[34] These calculations suggest that all three molecules prefer a common ground state conformation in which the sp^2-hybridized carbon of the heterocyclic ring is nearly eclipsing the H-9 proton of the cyclopentenyl ring. Such conformations would also place the 5-(chloromethyl) group of the heterocyclic systems in a position which would be advantageous toward nucleophilic attack

(32) DMSO-based pK_a data. Bordwell, F. G. Unpublished results (personal communication, 1994).

(33) Bordwell, F. G.; Algrim, D. J.; Harrelson, J. A., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 5903.

(34) For additional infomation on these calculations see: Smith, D. C. Ph.D. thesis, Purdue University, 1994.

Scheme 9[a]



[a] Reagents and conditions: (a) 6% Na/Hg, Na_2HPO_4, EtOH, rt, 12 h, 88%; (b) $NaBH_3CN$, AcOH, rt, 6 h, 78% yield of **31**; 83% yield of **32**; (c) TsOH, EtOH, rt, 8 h, 82%; (d) LiOH, $MeOH/H_2O$, rt, 75%.

Table 1. nOe Irradiations for Tricyclic amine **32**

Irradiate	Observe	% nOe
H_{11}	H_9	3%
H_9	H_{11}	3%
H_9	H_3	10%
H_3	H_9	12%
H_3	H_6	none
H_6	H_3	none

by intermediate α-sulfonyl anions generated by the addition of **11** to the vinyl sulfones. While these conformations provide insight into the relative success of the annulation event, they do little to explain why two of these three systems undergo competitive β-elimination of the heterocyclic units while the vinylogous urethane does not.

The main structural difference between bicyclics **20**, **23**, and **29** is the size of the exocyclic group (or atom) bonded to the sp^2-hybridized carbon of the each heterocyclic ring. In terms of steric demand, the vinylogous urethane moiety is the largest among the three exocyclic groups while the lactam oxygen is the smallest. If it is assumed that the larger exocyclic substituents may act to hinder free rotation about the C–N bond, it would follow that vinylogous urethane **23** would have access to fewer low energy conformations than either **20** or **29**. Extending this premise a step further, it would also be logical to assume that thioamide **20** would also have access to slightly fewer low energy conformations than lactam **29** due to the greater steric demand of the sulfur atom. Thus, it is possible that the presence of larger exocyclic groups may enforce conformations in which the chloromethyl group is in a position which favors S_N2 displacement of the chloride ion. On the other hand, smaller substituents may possess a greater level of free rotation about this C–N bond, thus placing the chloromethyl group in a position where it may not be readily disposed toward nucleophilic attack by the intermediate α-sulfonyl anion. In such an instance, it would be expected that elimination of the heterocyclic unit may become competitive with the required annulation event.

Since the tricyclic structure of sulfone **24** met all of the key bond requirements of pyrrolidine analog **9**, it was thought that this synthesis might be concluded by a simple and straightforward sequence of functional group interconversions. Thus, consideration was next given to reductive cleavage of the phenyl sulfone moiety. Employing the conditions of Trost,[35] tricyclic sulfone **24** was dissolved in ethanol buffered with Na_2HPO_4 and treated with an excess of 6% sodium amalgam for 12 h at room temperature (Scheme 9). Unexpectedly, isolation of this reaction product provided the known enyne **25** in 85–89% yield, while the required tricyclic vinylogous urethane was not in evidence. This represented an unprecedented event as these comparatively mild reaction conditions had been previously demonstrated to avoid problems associated with competitive β-elimination of the sulfone moiety.[6] Attempts at performing the cleavage at lower temperatures also failed to provide observable amounts of the required product, and conjugated enyne **25** was again isolated in high yield. It is postulated that ethoxide-mediated elimination of the homopropargylic sulfone is responsible for the formation of **25**. Applying the conditions of dissolving metal reduction,[36] Li/NH_3 in THF/t-BuOH at −90 °C, led to the formation of a complex reaction mixture, again with no formation of the requisite desulfonylated vinylogous urethane.

An alternative approach to **9** was to perform the 1,4-reduction of the vinylogous urethane moiety prior to attempting desulfonylation (Scheme 9). Accordingly, treatment of vinylogous urethane **24** with acetic acid and sodium cyanoborohydride[37] did provide the required tricyclic amine **31** in fair yield (78%); however, upon treating amino sulfone **31** with sodium amalgam in buffered ethanol at various reaction temperatures, a complex mixture of reaction products was obtained in a poor mass balance (~30%). Examination of this mixture

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(36) (a) Truce, W. E.; Tate, D. P.; Burdge, D. N. *J. Am. Chem. Soc.* **1960**, *82*, 2872. (b) Truce, W. E.; Breiter, J. J. *J. Am. Chem. Soc.* **1962**, *84*, 1621.
(37) Williams, D. R.; Sit, S.-Y. *J. Org.Chem.* **1982**, *47*, 2846–2851.

failed to indicate the presence of the anticipated tricyclic amine, and many of the side products still contained the intact phenyl sulfone moiety. While other options were available for effecting the desulfonylation of either **30** or **31**, it was decided to abandon the synthesis of pyrrolidine analog **9** and complete the synthesis of a pyrrolidine analog utilizing the readily available and somewhat unstable enyne **25**.

With this redefined synthetic goal in mind, it was decided to effect the required 1,4-reduction of the vinylogous urethane moiety (Scheme 9). Hence, vinylogous urethane **25** was treated with 2 equiv of acetic acid and 1 equiv of sodium cyanoborohydride[33] at room temperature for 6 h to provide pyrrolidine **32**, as a mixture of THP diastereomers, in 80–85% yield. This reaction proceeded with a high degree of stereoselectivity, as only a single stereoisomer was obtained as a result of this reduction. Assignment of the stereochemistry of **32** was accomplished through 1D NOE experiments performed on a 300 MHz NMR spectrometer. Partial saturation of the signals associated with the methine hydrogens α to the amine nitrogen (H_3, H_6, and H_9) and α to the silyl ether moiety (H_{11}) was performed, and these results are summarized in Table 1 (Scheme 9). Both H_3 and H_9 were found to give reciprocal NOE enhancements (10% and 12%), suggesting a close spatial relationship (molecular modeling of this structure predicted a distance of 2.3 Å). Partial saturation of H_6 failed to show any enhancement of H_3 (molecular modeling predicted a distance of 3.8 Å), thus suggesting a more remote relationship between these atoms. Had this reduction proceeded with introduction of hydride from the α face of this molecule, one would have expected to observe NOE enhancements between H_3 and H_6 and little to no enhancement between H_3 and H_9 (intramolecular distances predicted by molecular modeling were H_3–H_6, 2.5 Å, and H_3–H_9, 3.6 Å). Thus, based upon these results H_3 was assigned as having been delivered from the β-face of this molecule. Ironically, unlike enyne **25**, pyrrolidine **32** was amenable to long term storage, suggesting that perhaps the vinylogous urethane moiety was responsible for the instability of **25**.

With the desired stereochemistry established at C-3, the synthesis of this prostacyclin analog proceeded in a straightforward manner (Scheme 9). Thus, bis-ether deprotection was accomplished by treating pyrrolidine **32** with TsOH[38] at room temperature for 6 h and led to the isolation of ester diol **33** in 89–92% yield. Owing to the potential water solubility of the intended product, it was elected to isolate this material as its lithium salt. Thus, ester diol **33** was treated with an excess of lithium hydroxide in a 3:1 solution of methanol/water for 4 h at ambient temperature. Purification of this prostacyclin analog was achieved by reversed phase HPLC to provide pyrrolidine carboxylate **34** in 75% yield. In vitro testing of **34** as an inhibitor of collagen-induced platelet aggregation revealed it to be essentially inactive with an IC_{50} of >10 μM.[39]

Conclusion

We have reported the synthesis of a symchiral 1-azatricyclo[6.3.0.$0^{2,6}$]undec-5-enyl prostaglandin I_2 analog **34** which utilized vinyl sulfone methodology to construct the tricyclic framework. Introduction of the heterocyclic unit of **34** was accomplished by employing a novel S_N2'–thio-Claisen rearrangement coupling of an allylic substituted vinyl sulfone with a thiolactam. This synthesis was accomplished in seven steps from mesylate **22** in an overall yield of 27%. Compound **34** was essentially inactive as an inhibitor of collagen-induced platelet aggregation, having an IC_{50} of >10 μM.

Experimental Section[40]

(−)-(5*S*)-5-(Chloromethyl)-2-pyrrolidinone (12).[15] To 150 mL of dry CH_2Cl_2 was added 10.07 g (38.4 mmol) of triphenylphosphine ,and the reaction mixture was cooled to 0 °C. After 5 min, 5.54 g (41.5 mmol) of NCS was added to the solution in small portions while the temperature was maintained at <5 °C. The resulting purple solution was then stirred for an additional 10 min, and then 3.39 g (29.5 mmol) of alcohol **14** was added in small portions. The solution was permitted to warm to rt, and stirring was continued for 12 h. The reaction mixture was then diluted with 100 mL of saturated aqueous NH_4Cl. The aqueous phase was extracted with 3 × 100 mL portions of CH_2Cl_2, and the combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to provide a purple oil. Purification was accomplished by flash chromatography[41] using 60–200 mesh silica gel, eluting with 80% EtOAc/hexanes (Hex), 100% EtOAc, and 5% MeOH/CH_2Cl_2 to provide 3.31 g (84% yield) of chloride **12** as a pale yellow solid: R_f = 0.31 (100% EtOAc); mp 55–56 °C; IR ($CDCl_3$) 3432, 1702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (br s, 1H), 3.94 (m, 1H), 3.54 (dd, 1H, *J* = 4.9, 11.1), 3.47 (dd, 1H, *J* = 6.7, 11.1), 2.24–2.48 (m, 3H), 1.82–1.94 (m, 1H); APT[42] (75 MHz, $CDCl_3$) δ 178.1 (e), 55.3 (o), 48.0 (e), 29.7 (e), 24.6 (e); LRMS (CI, isobutane) *m*/*z* 134 ($M + H^+$, base); HRMS (CI, isobutane) exact mass calcd for C_5H_8ClNO + H 134.0373, found 134.0371; $[\alpha]_D$ = −20.7° (*c* = 0.374, EtOH).

(−)-(5*S*)-1-Aza-1-[(1′*S*,4′*R*)-4′-[(*tert*-butyldiphenylsilyl)oxy]-2′-(phenylsulfonyl)-2′-cyclopentenyl]-5-(chloromethyl)-2-cyclopentanone (10). A flame-dried flask was charged with 10 mL of dry THF and 171.7 mg (1.29 mmol) of symchiral lactam chloride **12**. The resulting solution was cooled to 0 °C, and to this reaction mixture was added 0.65 mL (0.65 mmol) of a 1.0 M solution of sodium bis(trimethylsilyl)amide (NaHMDS) in THF, in a dropwise fashion over 10 min. After being stirred for 30 min at 0 °C, the solution was cooled to −78 °C and a solution of the ammonium salt **13**[13] (394.9 mg, 0.65 mmol) in 4 mL of CH_2Cl_2 was added *via* cannula. The reaction was complete within 10 min of addition of **13**. The reaction mixture was quenched with 10 mL of saturated aqueous NH_4Cl. The aqueous phase was extracted with 4 × 35 mL portions of EtOAc, and the combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to afford a viscous off-white oil. Purification was accomplished *via* flash chromatography using 60–200 mesh silica gel, eluting with 1:1 EtOAc/Hex to afford 375.2 mg (95% yield) of desired bicyclic lactam **10** as a white foam and as a single diastereomer: R_f = 0.29 (7:13 EtOAc/Hex); IR ($CDCl_3$) 1692, 1318, 1156 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, 2H, *J* = 7.24), 7.36–7.68 (m, 13H), 6.73 (s, 1H), 4.98 (br s, 1H), 4.67 (m, 1H), 4.08 (m, 1H), 3.91 (dd, 1H, *J* = 2.59, 11.04), 3.54 (dd, 1H, *J* = 9.4, 10.85), 2.40–2.51 (m, 2H), 2.02–2.17 (m, 4H), 1.08 (s, 9H); APT (75 MHz, $CDCl_3$) δ 175.0 (e), 146.4 (o), 138.9 (e), 135.7 (o), 135.6 (o), 133.8 (o), 132.9 (e), 132.8 (e), 130.1 (o), 130.0 (o), 129.1 (o), 128.5 (o), 127.9 (o), 73.3 (o), 58.1 (o), 53.2 (o), 45.5 (e), 37.6 (e), 29.4 (e), 26.8 (o), 23.0 (e), 19.0 (e); LRMS (CI, isobutane) *m*/*z* 596 ($M + H^+$, 40.8), 594 ($M + H^+$, base), 536 (4.6), 516 (3.2), 338 (15.1), 304 (4.0), 257 (5.4); HRMS (CI, isobutane) exact mass calcd for $C_{32}H_{36}ClNO_4SSi$ + H 596.1901, found 594.1876; $[\alpha]_D$ = −37.7° (*c* = 0.092, $CHCl_3$).

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(39) Jakubowski, J. Personal communication, 1994. For the experimental protocol see: ref 6.
(40) For typical experimental protocols, see: Chiu, C. K.-F.; Govindan, S. V.; Fuchs, P. L. *J. Org. Chem.* **1994**, *59*, 311.
(41) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(42) Patt, S. L.; Shoolery, J. N. *J. Magn. Reson.* **1982**, *46*, 535.

(−)-(5*S*)-1-Aza-1-[(1′*S*,4′*R*)-4′-hydroxy-2′-(phenylsulfonyl)-2′-cyclopentenyl]-5-(chloromethyl)-2-cyclopentanone (16). To a solution of 102.7 mg (0.21 mmol) of thiolactam **20** in 5 mL of dry THF was added 92.8 mg (0.26 mmol) of benzene seleninic anhydride at rt, and the resulting mixture was permitted to stir for 4 h. After this interval, the reaction mixture was diluted with 10 mL of distilled water and 10 mL of CH_2Cl_2. The aqueous layer was extracted with 1 × 10 mL portions of CH_2Cl_2, and the combined organics were washed with 10 mL of saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated *in vacuo* to afford a yellow solid. Purification of the crude reaction mixture was accomplished by flash chromatography using 60−200 mesh silica gel, eluting with 3:1 EtOAc/Hex to afford 57 mg (76% yield) of lactam alcohol **16** as a white solid: R_f = 0.11 (7:13 EtOAc/Hex); mp 196−197 °C; IR ($CDCl_3$) 3320, 1675, 1305, 1150, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88−7.90 (m, 2H), 7.54−7.69 (m, 3H), 6.95 (ap t, 1H, *J* = 1.22), 5.61 (d, 1H, *J* = 11.62), 4.74 (m, 1H), 4.39 (d, 1H, *J* = 10), 4.03 (m, 1H), 3.72 (dd, 1H, *J* = 3.91, 12.15), 3.56 (dd, 1H, *J* = 2.78, 12.15), 2.87 (ddd, 1H, *J* = 7.82, 9.68, 15.35), 2.85 (m, 1H), 2.13 (d, 1H, *J* = 15.29), 1.74−1.81 (m, 2H), 1.52−1.62 (m, 1H); APT (75 MHz, $CDCl_3$) δ 175.6 (e), 147.6 (o), 141.6 (e), 139.4 (e), 133.8 (o), 129.2 (o), 127.5 (o), 73.9 (o), 61.4 (o), 56.0 (o), 46.6 (e), 40.0 (e), 30.3 (e), 21.4 (e); LRMS (CI, isobutane) *m*/*z* 358 (M + H^+, 33.2), 356 (M + H^+, base), 338 (17.0), 180 (11.6); HRMS (CI, isobutane) exact mass calcd for $C_{16}H_{18}ClNO_4S$ + H 356.0723, found 356.0717; $[\alpha]_D$ = −89.2° (*c* = 0.057, $CHCl_3$). Anal. Calcd for $C_{16}H_{18}ClNO_4S$: C, 54.01; H, 5.10; Cl, 9.96; N, 3.94. Found: C, 53.70; H, 5.44; Cl, 9.66; N, 3.93.

(−)-(5*S*)-5-(Chloromethyl)-2-thiopyrrolidinone (18).[17] To 350 mL of dry benzene was added 6.46 g (48.4 mmol) of lactam **12** and 22.6 g (55.9 mmol) of Lawesson's reagent, and the resulting heterogeneous mixture was stirred at rt for 12 h. The solution was then filtered, the cake was washed with 3 × 100 mL portions of benzene, and the combined mother liquors were concentrated *in vacuo* to afford an orange solid which was purified by flash chromatography using 60−200 mesh silica gel, eluting with 1:4 EtOAc/Hex, to provide a white solid which was recrystallized from hot $CHCl_3$/Hex to afford 5.82 g (80% yield) of thiolactam **18** as a clear, colorless crystalline solid: R_f = 0.41 (1:1, EtOAc/Hex); mp 126−128 °C; IR ($CDCl_3$) 3180, 1517, 1372, 1128 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.81 (br s, 1H), 4.23 (m, 1H), 3.63 (dd, 1H, *J* = 4.72, 11.38), 3.54 (dd, 1H, *J* = 6.76, 11.38), 2.96 (m, 2H), 2.41 (m, 1H), 1.98 (m, 1H); APT (75 MHz, $CDCl_3$) δ 206.2 (e), 62.9 (o), 46.4 (e), 42.8 (e), 26.8 (e); LRMS (EI, 70 eV) *m*/*z* 151 (M^+, 6.0), 149 (M^+, 22.3), 100 (base), 71 (27.2), 67 (52.7); HRMS (EI) exact mass calcd for C_5H_8ClNS 149.0066, found 149.0063; $[\alpha]_D$ = −36.2° (*c* = 0.051, $CHCl_3$). Anal. Calcd for C_5H_8ClNS: C, 40.13; H, 5.39; Cl, 23.69; N, 9.36; S, 21.43. Found: C, 40.03; H, 4.74; Cl, 23.98; N, 9.54; S, 21.30.

(−)-(5*S*)-1-Aza-1-[(1′*S*,4′*R*)-4′-[(*tert*-butyldiphenylsilyl)oxy]-2′-(phenylsulfonyl)-2′-cyclopentenyl]-5-(chloromethyl)cyclopentane-2-thione (20). A solution of 58.3 mg (0.38 mmol) of symchiral thiolactam **18** in 2 mL of dry CH_2Cl_2 was cooled to −78 °C with stirring under argon, and to this solution was added 115.4 mg (0.24 mmol) of symchiral ammonium salt **13** in 2 mL of dry CH_2Cl_2 *via* cannula. Stirring continued for 10 min at −78 °C, and the bath was removed. The reaction mixture was allowed to stir at rt for 12 h. The reaction was complete after 12 h, and the reaction mixture was diluted with 5 mL of CH_2Cl_2 and 5 mL of saturated aqueous NH_4Cl. The aqueous layer was extracted with 3 × 5 mL portions of CH_2Cl_2, and the combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to afford a pale yellow solid. Purification was accomplished by flash chromatography using 60−200 mesh silica gel, eluting with 1:4 EtOAc/Hex, to afford 107 mg (92% yield) of synfacial bicyclic thioamide **20** as a white solid: R_f = 0.31 (1:3 EtOAc/Hex); mp 136−137 °C; IR ($CDCl_3$) 1448, 1322, 1156, 1094 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, 2H, *J* = 7), 7.52−7.65 (m, 3H), 6.99 (s, 1H), 6.39 (d, 1H, *J* = 8.75), 4.79 (d, 1H, *J* = 7.2), 4.47 (m, 1H), 3.92 (ap d, 1H, *J* = 8.68), 3.46 (ap t, 1H, *J* = 10.85), 2.94−3.18 (m, 2H), 2.70 (ap p, 1H), 2.08−2.28 (m, 2H), 1.75 (d, 1H, *J* = 15.4), 0.91 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); APT (75 MHz, $CDCl_3$) δ 205.1 (e), 147.6 (o), 146.0 (e), 138.4 (e), 134.1 (o),129.1 (o), 129.0 (o), 72.2 (o), 63.7 (o), 57.3 (o), 43.5 (e), 42.5 (e), 39.2 (e), 25.7 (o), 25.4 (e), 18.0 (e), −4.7 (o), −5.0 (o); LRMS (CI, isobutane) *m*/*z* 488 (M + H^+, 17.1), 486 (M + H^+, 35.3), 337 (31.4), 207 (69.3), 150 (base), 143 (17.8), 133 (43.6); HRMS (CI, isobutane) exact mass calcd for $C_{22}H_{32}ClNO_3S_2Si$ + H 486.1360, found 486.1350; $[\alpha]_D$ = −194.1° (*c* = 0.104, $CHCl_3$). Anal. Calcd for $C_{22}H_{32}ClNO_3S_2Si$: C, 54.35; H, 6.63; Cl, 7.29; N, 2.88; S, 13.19. Found: C, 53.99; H, 6.35; Cl, 7.33; N, 3.03; S, 12.97.

(−)-(5*S*)-1-Aza-1-[(1′*S*,4′*R*)-4′-[(*tert*-butyldiphenylsilyl)oxy]-2′-(phenylsulfonyl)-2′-cyclopentenyl]-5-(chloromethyl)cyclopentane-2-thione (20) and (−)-(5*S*)-1-Aza-1-[(1′*R*,5′*R*)-5′-[(*tert*-butydimethylsilyl)oxy]-2′-(phenylsulfonyl)-2′-cyclopentenyl]-5-(chloromethyl)cyclopentane-2-thione (21). A mixture of 6.2 g (14.3 mmol) of mesylate **22**, 150 mL of dry toluene, and 3.12 g of poly(vinylpyridine) was cooled to −78 °C, 4.48 g (29.9 mmol) of symchiral thiolactam **18** was added, and the reaction mixture was allowed to gradually warm to rt overnight. After 14 h at rt the reaction was complete, the solution was filtered through a sintered glass funnel, and the cake was washed with 3 × 75 mL portions of toluene. The filtrate was concentrated *in vacuo*, and the crude yellow solid was purified by flash chromatography using 230−400 mesh silica gel, eluting with 10%, 15%, 25%, and 50% EtOAc/Hex to afford 5.85 g (84% yield) of the desired synfacial bicyclic thiolactam **20** (which gave spectral and physical characteristics identical to those reported above) as well as 158 mg (2.3% yield) of the regioisomeric bicyclic thiolactam **21** as a white foam: R_f = 0.38 (1:3 EtOAc/Hex); IR ($CDCl_3$) 1585, 1308, 1154, 1140 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, 2H, *J* = 8.16), 7.52−7.68 (m, 3H), 7.18 (ap t, 1H, *J* = 1.16), 6.13 (dd, 1H, *J* = 3.58, 8.44), 4.59 (dd, 1H, *J* = 8.06, 15.62), 4.17 (m, 1H), 3.88 (dd, 1H, *J* = 2.93, 11.32), 3.34 (ap t, 1H, *J* = 10.9), 3.03 (m, 2H), 2.93 (ddd, 1H, *J* = 3.27, 8.04, 19.01), 2.52 (ap ddt, 1H, *J* = 2.25, 7.06, 19.0), 2.14 (m, 2H), 0.81 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); APT (75 MHz, $CDCl_3$) δ 205.8 (e), 146.1 (o), 141.5 (e), 138.1 (e), 134.2 (o), 129.4 (o), 128.7 (o), 71.0 (o), 64.4 (o), 60.5 (e), 43.3 (e), 42.6 (e), 40.5 (e), 25.6 (o), 25.4 (e), 18.0 (e), −5.1 (o), −5.5 (o); LRMS (CI, isobutane) *m*/*z* 488 (M + H^+, 44.8), 486 (M + H^+, base), 470 (2.3); HRMS (CI, isobutane) calcd for $C_{22}H_{32}ClNO_3S_2Si$ + H 486.1360, found 486.1342; $[\alpha]_D$ = −18.6° (*c* = 0.010, $CHCl_3$).

(+)-Ethyl (2*E*)-2-[(3′*S*)-2′-Aza-2′-[(1″*S*,4′*R*)-4″-[(*tert*-butyldimethylsilyl)oxy]-2″-(phenylsulfonyl)-2″-cyclopentenyl]-3′-(chloromethyl)cyclopentylidene]ethanoate (23).[27] A solution of 4.83 g (9.9 mmol) of bicyclic thiolactam **20** in 20 mL of dry CH_3CN was cooled to 0 °C. To this reaction mixture was added dropwise a solution of 2.7 g (11.4 mmol) of carbethoxymethyl trifluoromethanesulfonate[26] in 3 mL of dry CH_3CN over 5 min. After 2.5 h and gradual warming to rt, alkylation was complete by TLC, the reaction mixture was diluted with 100 mL of dry CH_2Cl_2, and after the mixture was stirred for 10 min, 3.39 g (12.9 mmol) of triphenylphosphine was added. After an additional 5 min of stirring, 4.15 mL (29.8 mmol) of triethylamine was added and the reaction was stirred for an additional 12 h at rt. The reaction mixture was diluted with 100 mL of a 1.0 M solution of aqueous NaH_2PO_4. The aqueous phase was extracted with 3 × 100 mL portions of CH_2Cl_2, and the combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to afford a pale yellow solid. Purification was accomplished by flash chromatography using 60−200 mesh silica gel, eluting with 10, 15, and 20% EtOAc/Hex to afford 4.67 g (87% yield) of vinylogous urethane **23** as a pale yellow foam: R_f = 0.47 (2:3 EtOAc/Hex); IR ($CDCl_3$) 1684, 1596, 1308, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, 2H, *J* = 7.54), 7.4−7.58 (m, 3H), 6.96 (s, 1H), 4,85 (m, 1H), 4.69 (m, 1H), 4.48 (s, 1H), 3.89−3.99 (m, 3H), 3.47 (d, 2H, *J* = 4.43), 2.61−2.80 (m, 2H), 2.35 (ap dt, 1H, *J* = 5.27, 14.45), 1.70−1.89 (m, 2H), 1.17 (t, 3H, *J* = 7.1), 0.89 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H); APT (75 MHz, $CDCl_3$) δ 168.2 (e), 160.0 (e), 147.6 (o), 143.7 (e), 138.1 (e), 133.6 (o), 128.7 (o), 127.7 (o), 83.5 (o), 72.8 (o), 66.4 (o), 58.3 (o), 58.1 (e), 46.2 (e), 36.4 (e), 30.8 (e), 25.6 (o), 24.5 (e), 17.9 (e), 14.7 (o), −4.8 (o), −4.9 (o); LRMS (EI, 70 eV) *m*/*z* 541 (M^+, 6.2), 539 (M^+, 13.4), 482 (24), 400 (45.3), 398 (base), 352 (71.3), 266 (8.4), 195 (10.3); HRMS

(EI) exact mass calcd for $C_{26}H_{38}ClNO_5SSi$ 539.1929, found 539.1918; $[\alpha]_D = +7.72°$ (c = 0.023, $CHCl_3$).

(+)-Ethyl (2*E*)-2-[(3′*S*,5′*R*,6′S(1″*S*),7′*S*,9′*S*)-2′-Aza-5′-[(*tert*-butyldimethylsilyl)oxy]-6′-[1″-cyclohexyl-1″-(tetrahdropyranyloxy)prop-2″-yn-3″-yl]-7′-(phenylsulfonyl)tricyclo-[6.3.0.0^{3,7}]undecanylidene]ethanoate (24), (+)-Ethyl (2*E*)-2-[(3′*S*,5′*R*,6′(1″*S*),9′*S*)-2′-Aza-5′-[(*tert*-butyldimethylsilyl)oxy]-6′-[1″-cyclohexyl-1″-(tetrahdropyranyloxy)prop-2″-yn-3″-yl]tricyclo[6.3.0.0^{2,6}]undeca-6-enylidene]ethanoate (25). To a flame-dried flask containing 2.51 g (11.3 mmol) of acetylene **11**[10] and 150 mL of dry ether cooled to 0 °C was added 5.6 mL (11.5 mmol) of a 2.05 M solution of *n*-butyllithium (in hexanes) dropwise and stirring continued for an additional 10 min. The ice bath was removed and stirring continued for an additional 5 min, whereupon 1.9 mL (10.9 mmol) of HMPA was added and the resulting solution was stirred for an additional 5 min. The lithium acetylide solution was then cooled to −30 °C and transferred *via* cannula to a solution of vinyl sulfone **23** (1.97 g, 3.64 mmol) in 120 mL of ether maintained at a temperature of −30 °C. Stirring continued for 15 min, following which 100 mL of saturated aqueous NH_4Cl was added and the reaction mixture was permitted to warm to rt. The aqueous phase was extracted with 2 × 100 mL portions of EtOAc, and the combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to afford a brown oil. Purification of this crude oil was accomplished by flash chromatography, employing 230−400 mesh silica gel, eluting with 15−20% EtOAc/Hex to provide 2.30 g (87% yield) of tricyclic sulfone **24** (as an 8.6:1 inseparable mixture of THP diastereomers) as an amber oil. Characterization is made for the major THP diastereomer: R_f = 0.47 (2:3 EtOAc/Hex); IR ($CHCl_3$) 1678, 1598, 1306, 1142 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, 2H, J = 7.63), 7.54−7.68 (m, 3H), 5.17 (b m, 1H), 4.42 (bs, 1H), 4.38 (ap dd, 1H, J = 6.2, 8.4), 4.18 (dd, 1H, J = 1.4, 6.6), 4.12−4.05 (m, 3H), 3.87−3.75 (m, 2H), 3.61−3.46 (m, 2H), 2.98 (dd, 1H, J = 1.1, 9.9), 2.91 (m, 1H), 2.43 (m, 1H), 2.38−2.04 (m, 3H), 1.95−1.55 (m, 11H), 1.36−1.06 (m, t, 10H, J = 7.1), 0.81 (s, 9H), −0.05 (s, 3H), −0.11 (s, 3H); APT (75 MHz, $CDCl_3$) δ 168.6 (e), 161.2 (e), 137.3 (e), 134.2 (o), 130.8 (o), 129.0 (o), 95.2 (o), 85.9 (e), 83.5 (e), 80.5 (e), 80.4 (o), 75.2 (o), 69.6 (o), 62.8 (o), 62.2 (e), 59.5 (o), 58.5 (e), 46.0 (o), 42.6 (o), 39.5 (e), 38.5 (e), 34.7 (e), 30.4 (e), 29.1 (e), 29.0 (e), 28.4 (e), 26.4 (e), 26.0 (e), 25.9 (e), 25.6 (o), 25.5 (e), 19.4 (e), 17.9 (e), 14.7 (o), −4.8 (o), −4.9 (o); LRMS (CI, isobutane) m/z 726 (M + H$^+$, 20.8), 642 (15.1), 624 (13.1), 586 (21.6), 540 (32.8), 257 (46.2), 143 (base), 133 (86.7); HRMS (EI) exact mass calcd for $C_{40}H_{59}NO_7SSi$ 725.3782, found 725.3775; $[\alpha]_D$ = −12.3° (c = 0.044 $CHCl_3$). Tricyclic enyne **25** (oil) was isolated in 128 mg (6% yield) as a 6:1 mixture of inseparable THP diastereomers. Characterization is made for the major THP diastereomer: R_f = 0.55 (2:3 EtOAc/Hex); IR ($CDCl_3$) 1673, 1595 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99 (m, 1H), 4.91 (m, 1H), 4.53 (s, 1H), 4.34 (d, 1H, J = 6.7), 4.07 (m, 3H), 3.94 (ap b t, 1H), 3.78 (m, 2H), 3.51 (m, 1H), 2.94−2.78 (m, 3H), 2.29 (m, 1H), 1.98−1.52 (m, 15H), 1.26−1.05 (m, 8H), 0.90 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); APT (75 MHz, $CDCl_3$) δ 168.9 (e), 164.3 (e), 153.8 (e), 122.0 (e), 95.1 (o), 93.7 (e), 80.8 (o), 79.6 (o), 70.0 (o), 66.9 (o), 62.5 (o), 61.9 (e), 58.5 (e), 45.1 (e), 42.7 (o), 34.6 (e), 34.2 (e), 30.9 (e), 30.4 (e), 29.2 (e), 29.0 (e), 26.4 (e), 25.9 (e), 25.9 (e), 25.8 (o), 25.5 (e), 19.7 (e), 18.2 (e), 14.7 (o), −4.6 (o), −4.8 (o); LRMS (CI, isobutane) m/z 584 (M + H$^+$, 25.0), 446 (57.0), 133 (40.6), 85 (base); HRMS (CI, isobutane) exact mass calcd for $C_{34}H_{53}NO_5Si$ + H 584.3771, found 584.3748; $[\alpha]_D$ = +98.5° (c = 0.049, $CHCl_3$).

(−)-(2*S*,4*R*,5*S*(1′*S*),6*S*,8*S*)-1-Aza-4-[(*tert*-butyldimethylsilyl)oxy]-5-[1′-cyclohexyl-1′-(tetrahdropyranyloxy)prop-2′-yn-3′-yl]-6-(phenylsulfonyl)tricyclo[6.3.0.0^{2,6}]undecane-11-thione (26), (−)-(5*S*)-5-(Chloromethyl)-2-thiopyrrolidinone (18), and (−)-(1*R*,2*S*)-1-[(*tert*-butyldimethylsilyl)oxy]-2-[1′-cyclohexyl-1′-(tetrahdropyranyloxy)prop-2′-yn-3′-yl]-3-(phenylsulfonyl)cyclopentene (27). A flame-dried flask containing 321 mg (1.4 mmol) of acetylide **11**[10] in 20 mL of dry ether was cooled to 0 °C, and to this solution was added 0.46 mL (0.90 mmol) of a 1.95 M solution of *n*-butyllithium (in hexanes) dropwise. The resulting solution was stirred at 0 °C for 5 min, and then the bath was removed and stirring continued for an additional 5 min at rt. HMPA (0.16 mL, 0.90 mmol) was added and stirring continued for 5 min, and then the resulting solution was recooled to 0 °C and transferred *via* cannula to a solution of 144 mg (0.30 mmol) of bicyclic thiolactam **20** in 20 mL of dry ether cooled to −30 °C. After 15 min, 10 mL of saturated aqueous NH_4Cl was added, and the resulting mixture was warmed to rt. The aqueous phase was extracted with 2 × 30 mL portions of EtOAc, and the combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to afford an amber oil. Purification of the crude material was achieved *via* flash chromatography, employing 60−200 mesh silica gel and eluting with 15% EtOAc/Hex to provide 4.4 mg (10% yield) of monocyclic thiolactam **18**, which gave physical and spectral characteristics identical to those previously reported. In addition, 15 mg (9% yield) of acetylenic vinyl sulfone **27** (as a 9:1 inseparable mixture of THP diastereomers) was isolated as a pale yellow oil. Characterization is made for the major THP diastereomer: R_f = 0.54 (2:3 EtOAc/Hex); IR ($CDCl_3$) 1310, 1150, 1090 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, 2H, J = 7.1), 7.63−7.48 (m, 3H), 6.84 (br d, 1H, J = 1.6), 4.82 (ap t, 1H, J = 3.2), 4.48 (m, 1H), 4.0 (dd, 1H, J = 1.79, 6.66), 3.84−3.73 (m, 2H), 3.52−3.44 (m, 3H), 2.95−2.86 (m, 1H), 2.53−2.38 (m, 1H), 1.94−0.83 (m, 15H), 0.79 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); APT (75 MHz, $CDCl_3$) δ 149.4 (e), 142.2 (o), 139.9 (e), 133.3 (o), 129.0 (o), 128.2 (o), 95.1 (o), 82.7 (e), 82.0 (e), 80.6 (o), 69.6 (o), 62.1 (e), 45.2 (o), 42.6 (o), 41.6 (e), 30.5 (e), 29.1 (e), 28.8 (e), 26.5 (e), 26.0 (e), 25.9 (e), 25.6 (o), 25.5 (e), 19.3 (e), 17.9 (e), −4.8 (o), −5.0 (o); LRMS (CI, isobutane) m/z 559 (M + H$^+$, 0.3), 541 (0.9), 487 (0.8), 457 (base), 325 (55.8) 85 (8.8); HRMS (CI, isobutane) exact mass calcd for $C_{31}H_{46}O_5SSi$ + H 559.2914, found 559.2891; $[\alpha]_D$ = −76.1° (c = 0.02, $CHCl_3$). Finally, 132.4 mg (67% yield) of tricyclic thiolactam **26** was isolated (as a 10:1 mixture of THP diastereomers) as a colorless oil. Characterization is made for the major THP diastereomer: R_f = 0.49 (4:6 EtOAc/Hex); IR (CH_2Cl_2) 1480, 1310, 1144, 1080 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, 2H, J = 7.7), 7.71−7.56 (m, 3H), 5.18 (br s, 1H), 5.02 (dd, 1H, J = 6.9, 8.4), 4.43 (m, 1H), 4.23 (dd, 1H, J = 1.38, 6.58), 3.86−3.79 (m, 1H), 3.68 (dd, 1H, J = 8.6, 15.8), 3.56 (m, 1H), 3.16−2.98 (m, 3H), 2.61 (ddd, 1H, J = 6.8, 8.8, 13.8), 2.44−2.26 (m, 3H), 2.04−1.09 (m, 17H), 0.93 (s, 9H), 0.05 (s, 3H), −0.09 (s, 3H); APT (75 MHz, $CDCl_3$) δ 197.6 (e), 136.9 (e), 134.3 (o), 130.7 (o), 129.2 (o), 95.2 (o), 85.4 (e), 82.3 (e), 80.0 (e), 75.2 (o), 69.6 (o), 65.7 (o), 62.1 (e), 59.9 (o), 48.9 (e), 46.9 (o), 42.6 (o), 38.8 (e), 38.7 (e), 30.4 (e), 29.1 (e), 29.0 (e), 28.9 (e), 26.4 (e), 26.0 (e), 25.9 (e), 25.6 (o), 25.5 (e), 19.4 (e), 17.9 (e), −4.8 (o), −4.9 (o); LRMS (CI, isobutane) m/z 672 (M + H$^+$, 2.1), 588 (70.0), 570 (43.5), 448 (76.7), 430 (10.1), 143 (base); HRMS (CI, isobutane) exact mass calcd for $C_{36}H_{53}NO_5S_2Si$ + H 672.3213, found 672.3199; $[\alpha]_D$ = −56.7° (c = 0.027, $CHCl_3$).

(−)-(5*S*)-1-Aza-1-[(1′*S*,4′*R*)-4′-[(*tert*-butyldimethylsilyl)oxy]-2′-(phenylsulfonyl)-2′-cyclopentenyl]-5-(chloromethyl)-2-cyclopentanone (29). A solution of 57 mg (0.17 mmol) of lactam alcohol **28** was dissolved in 2 mL of dry CH_2Cl_2, and the resulting solution was cooled to 0 °C. To this solution was added 47 μL (0.33 mmol) of triethylamine, followed by 50 μL (0.22 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate. After 30 min the reaction mixture was diluted with 5 mL of CH_2Cl_2 and 5 mL of saturated aqueous $NaHCO_3$. The aqueous phase was extracted with 3 × 5 mL portions of CH_2Cl_2, and the combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to provide a viscous oil. Purification was accomplished by flash chromatography employing 60−200 mesh silica gel, eluting with 3:7 EtOAc/Hex to afford 70.4 mg (88% yield) of silyl ether **29** as a colorless film: R_f = 0.24 (7:13 EtOAc/Hex); IR ($CDCl_3$) 1690, 1330, 1310, 1150 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95−7.99 (m, 2H), 7.52−7.66 (m, 3H), 6.87 (m, 1H), 5.15 (br s, 1H), 4.75 (ap dt, 1H, J = 2.66, 7.39), 4.01 (m, 1H), 3.81 (dd, 1H, J = 3.34, 10.82), 3.41 (dd, 1H, J = 9.96, 10.53), 2.59 (ddd, 1H, J = 7.55, 9.03, 14.63), 2.39−2.52 (m, 1H), 1.99−2.17 (m, 4H), 0.90 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); APT (75 MHz, $CDCl_3$) δ 175.1 (e), 146.4 (o), 145.7 (e), 138.9 (e), 133.9 (o), 129.1 (o), 128.6 (o), 72.5 (o), 58.0 (o), 53.1 (o), 45.1 (e), 38.1 (e), 29.2 (e), 25.8 (o), 22.9 (e), 18.1 (e), −4.7 (o), −4.9 (o); LRMS (CI, isobutane) m/z 472 (M +

H^+, 0.6), 470 (M + H^+, 1.5), 356 (base), 338 (16.9), 180 (1.8); HRMS (CI, isobutane) exact mass calcd for $C_{22}H_{32}ClNO_4SSi$ + H 470.1588, found 470.1574; $[\alpha]_D = -64.4°$ (c = 0.014, $CHCl_3$).

(−)-(5*S*)-5-(Chloromethyl)-2-pyrrolidinone (12), (−)-(2*S*,4*R*,5*S*(1′*S*),6*S*,8*S*)-1-Aza-4-[(*tert*-butyldimethylsilyl)oxy]-5-[1′-cyclohexyl-1′-(tetrahdropyranyloxy)prop-2′-yn-3′-yl]-6-(phenylsulfonyl)tricyclo[6.3.0.0^{2,6}]undecan-11-one (30) and (−)-(1*R*,2*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-[1′-cyclohexyl-1′-tetrahdropyranyloxy)prop-2′-yn-3′-yl]-3-(phenylsulfonyl)cyclopentene (27). A flame-dried flask containing 94.4 mg (0.42 mmol) of acetylide **11**[10] in 5 mL of dry ether was cooled to 0 °C, and to this solution was added 0.17 mL (0.32 mmol) of a 1.89 M solution of *n*-butyllithium (in hexanes) dropwise. The resulting solution was stirred at 0 °C for 5 min, and the bath was removed and stirring continued for an additional 5 min at rt, following which 96 μL (0.45 mmol) of HMPA was added and stirring was continued for an additional 5 min. The resulting solution was cooled to 0 °C and transferred *via* cannula to a solution of 49.8 mg (0.11 mmol) of bicyclic lactam **29** in 5 mL of dry ether cooled to −30 °C. Complete addition was achieved in 15 min, and 10 mL of saturated aqueous NH_4Cl was added, and the mixture was warmed to rt. The aqueous phase was extracted with 2 × 10 mL portions of EtOAc, the combined organics were dried over Na_2SO_4, and the solution was concentrated *in vacuo* to afford an amber oil. Purification of the crude material was achieved *via* flash chromatography, employing 60−200 mesh silica gel and eluting with 2:3 EtOAc/Hex to provide 3.4 mg (22% yield) of monocyclic lactam **12**, which gave physical and spectral properties identical to those previously reported. Also, 12.1 mg (19% yield) of acetylenic vinyl sulfone **27** was isolated (as a 9:1 inseparable mixture of THP diastereomers) as a pale yellow oil which also gave physical and spectral characteristics identical to those previously reported. In addition, 35.4 mg (51% yield) of tricyclic lactam **30** (as a 9:1 inseparable mixture of THP diastereomers) was isolated as an amber foam. Characterization is made for the major THP diastereomer: R_f = 0.10 (7:13 EtOAc/Hex); IR (CH_2Cl_2) 1688, 1308, 1144 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, 2H, J = 7.5), 7.67 (t, 1H, J = 7.1), 7.58 (dd, 2H, J = 7.1, 7.5), 5.19 (ap t, 1H, J = 3.3), 4.80 (ap t, 1H, J = 8.0), 4.45 (dd, 1H, J = 1.7, 6.7), 4.14 (m, 1H), 3.83 (m, 1H), 3.62−3.55 (m, 2H), 2.94 (dd, 1H, J = 1.7, 9.6), 2.56 (m, 1H), 2.45 (ddd, 1H, J = 6.7, 8.9, 13.4), 2.33 (m, 2H), 2.21 (dd, 1H, J = 9.8, 13.2), 2.0−1.5 (m, 8H), 1.3−1.1 (m, 7H), 0.89 (s, 9H), 0.23 (s, 3H), 0.51 (s, 3H); APT (75 MHz, $CDCl_3$) δ 173.6 (e), 137.0 (e), 134.0 (e), 130.9 (e), 129.0 (e), 95.3 (e), 85.1 (e), 81.9 (e), 80.4 (e), 74.8 (e), 69.6 (e), 62.2 (e), 58.7 (e), 57.2 (e), 46.6 (e), 42.6 (e), 39.8 (e), 39.8 (e), 33.0 (e), 30.4 (e), 29.1 (e), 29.0 (e), 26.4 (e), 26.0 (e), 25.9 (e), 25.6 (e), 25.6 (e), 24.8 (e), 19.4 (e), 17.9 (e), −4.8 (e), −4.9 (e); LRMS (CI, isobutane) m/z 572 (M + H − THP^+, 4.0), 554 (5.3), 458 (9.8), 440 (10.9), 318 (23.7), 143 (base); HRMS (EI) exact mass calcd for $C_{27}H_{36}NO_5SSi$ (M − t-butyl − THP^+) 514.2083, found 514.2075; $[\alpha]_D = -72.4°$ (c = 0.014, $CHCl_3$).

(+)-Ethyl (2*E*)-2-[(3′*S*,5′*R*,6′(1″*S*),9′*S*)-2′-Aza-5′-[(*tert*-butyldimethylsilyl)oxy]-6′-[1″-cyclohexyl-1″-(tetrahdropyranyloxy)prop-2″-yn-3″-yl]tricyclo[6.3.0.0^{3,7}]undeca-6-enylidene]ethanoate (25).[32] A solution of 3.18 g (8.30 mmol) of 6% Na/Hg, 20 mL of absolute ethanol, and 610 mg (4.3 mmol) of Na_2HPO_4 was cooled to 0 °C, and 589 mg (0.81 mmol) of vinylogous urethane **24** was added to the reaction mixture in small portions over 10 min. The reaction mixture was stirred for 1 h at 0 °C and stirred overnight at rt. The reaction mixture was cooled to 0 °C, 20 mL of saturated aqueous NH_4Cl and 20 mL of CH_2Cl_2 were added, and the mixture was warmed to rt. The aqueous phase was extracted with 3 × 20 mL portions of CH_2Cl_2, and the combined organics were dried over Na_2SO_4. The solvent was removed *in vacuo* to provide a brown oil which was purified by flash chromatography using 60−200 mesh silica gel and eluting with 10−20% EtOAc/Hex to provide 418 mg (88% yield, as a 7:1 mixture of inseparable THP diastereomers) of tricyclic enyne **25**. This material displayed spectral and physical characteristics identical to those reported previously.

(−)-Ethyl 2-[(1′*S*,3′*S*,5′*R*,6′*S*(1″*S*),7′*S*,9′*S*)-2′-Aza-5′-[(*tert*-butyldimethylsilyl)oxy]-6′-[1″-cyclohexyl-1″-(tetrahdropyranyloxy)prop-2″-yn-3″-yl]-7′-(phenylsulfonyl)tricyclo-[6.3.0.0^{3,7}]undecanyl]ethanoate (31).[34] A solution of 46.9 mg (0.065 mmol) of vinylogous urethane **24**, 5 mL of absolute ethanol, and 10 μL (0.17 mmol) of acetic acid was cooled to 0 °C, and to this solution was added 7.2 mg (0.11 mmol) of sodium cyanoborohydride and stirring continued for 4 h with gradual warming to rt. Then, 5 mL of saturated aqueous $NaHCO_3$ and 5 mL of CH_2Cl_2 were added, the aqueous phase was extracted with 3 × 5 mL portions of CH_2Cl_2, and the combined organics were dried over Na_2SO_4. The resulting solution was concentrated *in vacuo* to afford a colorless oil which was purified by flash chromatography using 60−200 mesh silica gel and eluting with 2:3 EtOAc/Hex to afford 37 mg (78% yield, as an 11:1 mixture of THP diastereomers) of tricyclic amine **31** as a colorless film. Characterization was made for the major THP diastereomer: R_f = 0.36 (2:3 EtOAc/Hex); IR ($CDCl_3$) 1728, 1304, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, 2H, J = 7.8), 7.65−7.52 (m, 3H), 5.15 (m, 1H), 4.2−4.09 (m, 4H), 3.84−3.50 (m, 4H), 3.33 (m, 1H), 2.84 (d, 1H, J = 10.1), 2.23−1.4 (m, 20H), 1.39−0.91 (m, 10H), 0.81 (s, 9H), −0.02 (s, 3H), −0.05 (s, 3H); APT (75 MHz, $CDCl_3$) δ 171.8 (e), 143.1 (e), 138.8 (e), 133.5 (o), 130.7 (o), 128.6 (o), 95.2 (o), 83.9 (e), 82.6 (e), 81.9 (e), 74.2 (o), 69.6 (o), 67.8 (o), 63.8 (o), 62.2 (e), 60.2 (e), 59.8 (o), 46.4 (o), 42.6 (o), 42.3 (e), 30.4 (e), 30.4 (e), 29.1 (e), 28.9 (e), 27.7 (e), 26.4 (e), 26.0 (e), 25.9 (e), 25.8 (o), 25.7 (o), 25.6 (e), 19.5 (e), 17.9 (e), 14.2 (o), −4.7 (o), −4.9 (o); LRMS (CI, isobutane) m/z 728 (M + H^+, 33.1), 644 (13.7), 626 (79.0), 393 (42.3), 223 (18.4), 207 (18.8), 189 (59.1), 171 (base), 143 (30.7); HRMS (CI, isobutane) exact mass calcd for $C_{40}H_{61}NO_7SSi$ + H 728.4016, found 728.3994; $[\alpha]_D = -87.2°$ (c = 0.014, $CHCl_3$).

(+)-Ethyl 2-(1′*S*,3′*S*,5′*R*,6′(1″*S*),9′*S*)-2′-Aza-5′-[(*tert*-butyldimethylsilyl)oxy]-6′-[1″-cyclohexyl-1″-(tetrahdropyranyloxy)prop-2″-yn-3″-yl]tricyclo[6.3.0.0^{3,7}]undeca-6-enyl]ethanoate (32).[34] A solution of 82 mg (0.14 mmol) of vinylogous urethane **25**, 8 mL of absolute ethanol, and 20 μL (0.35 mmol) of acetic acid was cooled to 0 °C, and to this solution was added 33.8 mg (0.54 mmol) of sodium cyanoborohydride in one portion. The reaction mixture was stirred for 30 min at 0 °C and then allowed to gradually warm to rt. After 4 h at rt, the reaction mixture was diluted with 10 mL of CH_2Cl_2 and 10 mL of saturated aqueous $NaHCO_3$. the aqueous phase was extracted with 3 × 10 mL portions of CH_2Cl_2, and the combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to afford a viscous amber oil. Purification was accomplished by flash chromatography, employing 60−200 mesh silica gel and eluting with 1:3 EtOAc/Hex to afford 68 mg (83% yield, as a 10:1 mixture of inseparable THP diastereomers) of tricyclic amine **32** as a pale amber oil. Characterization was made for the major THP diastereomer: R_f = 0.45 (2:3 EtOAc/Hex); IR ($CDCl_3$) 1726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.42 (br s, 1H), 4.85 (br s, 1H), 4.67 (d, 1H, J = 6.5), 4.06−3.94 (m, 2H), 3.82−3.74 (m, 1H), 3.54−3.44 (m, 2H), 3.33 (ap b t, 1H, J = 7.0), 3.18 (m, 1H), 2.65−2.52 (m, 2H), 2.39 (dd, 1H, J = 6.9, 15.0), 2.21−2.14 (m, 3H), 1.94−1.50 (m, 12H), 1.47−1.16 (m, 9H), 1.04 (s, 9H), 1.00 (t, 3H, J = 7.3), 0.26 (s, 3H), 0.16 (s, 3H); APT (75 MHz, $CDCl_3$) δ 171.7 (e), 157.5 (e), 152.7 (e), 95.1 (o), 92.3 (e), 81.6 (e), 81.0 (o), 71.5 (o), 70.3 (o), 67.3 (o), 63.7 (o), 61.6 (e), 60.0 (e), 47.2 (e), 43.4 (o), 41.8 (e), 34.1 (e), 33.1 (e), 32.8 (e), 30.8 (e), 29.6 (e), 29.5 (e), 26.9 (e), 26.5 (e), 26.4 (e), 26.1 (o), 26.0 (e), 19.5 (e), 18.4 (e), 14.3 (o), −3.0 (o), −4.4 (o); LRMS (EI) m/z 585 (M^+, base), 528 (15.4), 500 (18.0), 484 (23.0), 320 (9.4), 156 (32.2), 85 (36.6), 75 (36.1); HRMS (EI) exact mass calcd for $C_{34}H_{55}NO_5Si$ 585.3850, found 585.3851; $[\alpha]_D = +21.3°$ (c = 0.008, $CHCl_3$).

(+)-Ethyl 2-[(1′*S*,3′*S*,5′*R*,6′(1″*S*),9′*S*)-2′-Aza-5′-hydroxy-6′-(1″-cyclohexyl-1″-hydroxy-2″-yn-3″-yl)tricyclo[6.3.0.0^{3,7}]-undeca-6-enyl]ethanoate (33).[35] A solution of 79.4 mg (0.14 mmol) of diether **32**, 5 mL of absolute ethanol, and 29 mg (0.15 mmol) of *p*-toluenesulfonic acid was stirred at rt for 8 h. The reaction mixture was diluted with 5 mL of CH_2Cl_2 and 5 mL of saturated aqueous $NaHCO_3$, the aqueous phase was extracted with 3 × 5 mL portions of CH_2Cl_2, and the combined organics were dried over Na_2SO_4. The solvent was then

removed *in vacuo* to afford a pale yellow oil which was purified by flash chromatography employing 60–200 mesh silica gel and eluting with 75–100% EtOAc/Hex to afford 43 mg (82% yield) of ester diol **33** as a colorless film: $R_f = 0.16$ (1:1 EtOAc/Hex); IR ($CDCl_3$) 3687, 3612, 1745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.78 (br s, 1H), 4.27 (d, 1H, $J = 6.1$), 4.13 (q, 2H, $J = 7.8$), 3.92 (m, 1H), 3.64 (br m, 1H), 3.52 (br s, 2H), 3.39 (m, 1H), 2.81–2.66 (m, 2H), 2.56 (dd, 1H, $J = 7.2, 15.6$), 2.38 (dd, 1H, $J = 9.0, 15.6$), 2.30–2.06 (m, 3H), 1.87–1.52 (m, 8H), 1.28–0.76 (m, 9H); APT (75 MHz, $CDCl_3$) δ 171.9 (e), 154.9 (o), 119.2 (e), 95.4 (e), 80.4 (o), 79.2 (e), 71.6 (o), 67.8 (o), 67.2 (o), 63.7 (o), 60.5 (e), 44.1 (o), 44.0 (e), 40.5 (e), 34.1 (e), 32.5 (e), 28.8 (e), 28.3 (e), 26.4 (e), 25.9 (e), 14.2 (o); LRMS (CI, isobutane) m/z 388 ($M + H^+$, base), 370 ($M - H_2O^+$, 60.8), 335 (8), 363 (3.8), 156 (2.9); HRMS (CI, isobutane) exact mass calcd for $C_{23}H_{33}NO_4 + H$ 388.2488, found 388.2481; $[\alpha]_D = +62.8$ ($c = 0.005$, $CHCl_3$).

(+)-Lithium 2-[(1′*S*,3′*S*,5′*R*,6′(1″*S*),9′*S*)-2′-Aza-5′-hydroxy-6′-(1″-cyclohexyl-1″-hydroxy-2″-yn-3″-yl)tricyclo[6.3.0.0^{3,7}]-undeca-6-enyl]ethanoate (34). A solution of 2 mL of methanol, 0.5 mL of distilled water, 17.1 mg of ester **33**, and 6 mg of $LiOH·H_2O$ was allowed to stir for 8 h at rt. The crude reaction mixture was concentrated *in vacuo*, diluted with 0.5 mL of methanol, and filtered through a column of lipophilic sephadex (LH-20 grade) to remove the excess lithium hydroxide. Next, this material was purified by preparative HPLC using a C-8 column, eluting with a 15–70% CH_3CN/H_2O gradient (flow rate 1.2 mL/min), to afford 12 mg (75% yield) of the lithium carboxylate **34** as a colorless film: $R_f = 0.09$ (1:9 $MeOH/CH_2Cl_2$); IR (KBr pellet) 3696, 3650, 2005, 1641 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 4.93 (br s, 3H, O-H exchanges with CD_3OD), 4.35 (m, 1H), 4.23 (d, 1H, $J = 6.3$), 4.17 (m, 1H), 3.74 (m, 1H), 3.08–2.92 (m, 2H), 2.57–2.29 (m, 5H), 2.00-1.48 (m, 10H), 1.33–1.06 (m, 5H); APT (75 MHz, $CDCl_3$) δ 182.6 (e), 125.2 (e), 98.6 (e), 80.9 (o), 78.6 (e), 72.3 (o), 71.8 (o), 68.1 (o), 67.0 (o), 45.6 (e), 41.6 (o), 37.1 (e), 33.5 (e), 32.0 (e), 31.9 (e), 29.9 (e), 29.4 (e), 27.6 (e), 27.1 (e); FABMS (DTT/DTE) 552 ($M + DTT + K^+$, 23), 536 ($M + DTT + Na^+$, 46), 520 ($M + DTT + Li^+$, 12), 398 ($M + K^+$, 32), 382 ($M + Na^+$, 86), 366 ($M + Li^+$, 36), 360 ($M + H^+$, 41), 177 (53), 159 (49), 128 (base), 103 (71), 85 (93); HRMS (FAB, DTT/DTE) exact mass calcd for $C_{21}H_{29}NO_4 + H$ 360.2175, found 360.2155; $[\alpha]_D = +20.8°$ ($c = 0.002$, MeOH).

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Supplementary Material Available: Copies of the ^1H NMR and ^{13}C NMR of previously unreported compounds (58 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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